Co-administered drug	Effect of co-administration with DRV/RTV	Recommendation
Corticosteroids, systemic/inhaled/ nasal: budesonide, fluticasone, prednisone, dexamethasone	Increased exposure to budesonide, fluticasone, prednisolone DRV exposure may be reduced by dexamethasone due to CYP3A inhibition	Increased plasma levels of corticosteroids may occur with concurrent protease inhibitor use, even with inhaled and nasal administration, and may lead to side effects including Cushing's syndrome and adrenal suppression
Bosentan	Increased bosentan exposure	Cease bosentan at least 36 hours before initiation of DRV–RTV Wait at least 10 days after initiation of DRV–RTV to resume bosentan at 62.5 mg once daily or every other day, depending on patient tolerability
Immunosuppressants: cyclosporine, everolimus, sirolimus, tacrolimus	Increased exposure to immunosuppressants	Therapeutic drug monitoring of immunosuppressant drug recommended Co-administration of everolimus and DRV–RTV not recommended
Sedatives/hypnotics: buspirone, clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam, zolpidem	Increased exposure to sedatives	Clinical monitoring recommended, especially with midazolam, given potential for respiratory depression and prolonged sedation Use of oral midazolam or triazolam with DRV is contraindicated
Oral contraceptive pill: ethinyl oestradiol and norethindrone	Reduced exposure to ethinyl oestradiol and norethindrone	Alternative contraception methods recommended
Methadone, buprenorphine/naloxone	Methadone exposure reduced Buprenorphine exposure unchanged Levels of metabolite, norbuprenorphine increased	Monitor clinically Dose adjustments for methadone and buprenorphine may be needed
Antidepressants: paroxetine, sertraline, amitriptyline, desipramine, imipramine, nortriptyline and trazodone	Exposure to SSRIs including paroxetine and sertraline reduced Exposure to amitriptyline, desipramine, imipramine, nortriptyline, and trazodone may be increased	Clinical monitoring recommended Dose adjustment of antidepressant may be necessary
Anticonvulsants: phenobarbital, phenytoin, carbamazepine	Decreased plasma concentration of DRV due to cytochrome P-450 induction with phenobarbital and phenytoin DRV levels unchanged by carbamazepine Carbamazepine exposure increased by darunavir	Co-administration of phenytoin or phenobarbital with DRV–RTV contraindicated When co-administered with DRV, increased clinical and therapeutic drug monitoring of carbamazepine may be needed

Abbreviations: DRV: darunavir; RTV: ritonavir; INR: international normalized ratio; SSRI: selective serotonin reuptake inhibitor.
Source: Data compiled from de Meyer *et al.* (2008) and Stanford Univeristy (2014).

6b. Rash and severe cutaneous reactions

Although darunavir-associated rash is relatively common, occurring in up to 11% of patients in one observational study, the drug can usually be continued with the use of antihistamines or oral steroids (Nishijima *et al.*, 2014). Darunavir boosted with ritonavir (800/100 mg) administered once daily is associated with a higher rate of skin rash than other protease inhibitor–containing regimens, as reported in a study of Taiwanese patients (Lin *et al.*, 2014). During premarketing studies, rash occurred in 10.3% of patients treated with boosted darunavir, although causality was not established in all cases (Janssen, 2015b). The rash tends to develop early, within the first month of treatment, and is usually mild to moderate, allowing continuation of treatment with darunavir. The rash may occur more commonly in patients with early HIV infection (Nishijima *et al.*, 2014).

Because darunavir contains a sulfonamide moiety, it should be used with caution in patients with sulfonamide allergies. In a study of 405 patients taking a darunavir-containing regimen, 79 (17.5%) patients had a past history of allergic reaction to trimethoprim–sulfamethoxazole. Of these, an allergic reaction to darunavir was seen in 4 (5.1%) patients, versus 4 (1.2%) without a cotrimoxazole allergy, suggesting that cross-reactivity between darunavir and cotrimoxazole is uncommon but may be increased in those with previous cotrimoxazole allergy (Buijs *et al.*, 2015).

During clinical development studies, severe cutaneous and soft tissue reactions occurred in 0.4% of subjects treated with darunavir, whereas the rate of Stevens-Johnson syndrome